Insular Cortical Ischemia Is Independently Associated With Acute Stress Hyperglycemia

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Background and Purpose—Acute poststroke hyperglycemia has been associated with larger infarct volumes and a cortical location, regardless of diabetes status. Stress hyperglycemia has been attributed to activation of the hypothalamic-pituitary-adrenal axis but never a specific cortical location. We tested the hypothesis that damage to the insular cortex, a site with autonomic connectivity, results in hyperglycemia reflecting sympathoadrenal dysregulation.

Methods—Diffusion-weighted MRI, glycosylated hemoglobin (HbA1c), and blood glucose measurements were obtained in 31 patients within 24 hours of ischemic stroke onset. Acute diffusion-weighted imaging (DWI) lesion volumes were measured, and involvement of the insular cortex was assessed on T2-weighted images.

Results—Median admission glucose was significantly higher in patients with insular cortical ischemia (8.6 mmol/L; n = 14) compared with those without (6.5 mmol/L; n = 17; P = 0.006). Multivariate linear regression demonstrated that insular cortical ischemia was a significant independent predictor of glucose level (P = 0.001), as was pre-existing diabetes mellitus (P = 0.008). After controlling for the effect of insular cortical ischemia, DWI lesion volume was not associated with higher glucose levels (P = 0.849). There was no association between HbA1c and glucose level (P = 0.737).

Conclusions—Despite the small sample size, insular cortical ischemia appeared to be associated with the production of poststroke hyperglycemia. This relationship is independent of pre-existing glycemic status and infarct volume. Neuroendocrine dysregulation after insular ischemia may be 1 aspect of a more generalized acute stress response. Future studies of poststroke hyperglycemia should account for the effect of insular cortical ischemia. (Stroke. 2004;35:1886-1891.)

Key Words: glucose ■ hyperglycemia ■ stroke, acute ■ magnetic resonance imaging, diffusion-weighted

Hyperglycemia is present in 20% to 40% of patients with acute ischemic stroke, regardless of a history of diabetes mellitus.1,2 The presence of hyperglycemia, regardless of diabetes status, is associated with increased mortality and morbidity, greater stroke severity, and larger infarct volumes measured on cerebral computed tomography (CT) scan.1–7 This may reflect the association between elevated lactate and impaired penumbral salvage.8 It has been demonstrated that persistent poststroke hyperglycemia predicts infarct expansion and worse clinical outcome independent of premorbid glycemic status.9

As a biological marker of glycemic homeostasis, hyperglycemia and elevated glycosylated hemoglobin (HbA1c) have been used to diagnose and define poorly controlled diabetes.10 Currently, there is no accepted definition of stress hyperglycemia.2 Elevated blood glucose in the presence of normal HbA1c, regardless of diabetes status, may therefore represent a stress response. Stress hyperglycemia has been reported in 5% to 36% of acute stroke patients.1,3 The etiology and duration of hyperglycemia relative to the ischemic brain insult remains unclear. It may reflect elevated sympathoadrenal tone, increased stress hormones such as cortisol and noradrenaline, or damage to central autonomic control sites.6,11–13 The rise and fall of glucose after stroke parallels a neuroendocrine release profile.12 Stress hyperglycemia in acute stroke may be caused by either severe or catastrophic stroke, or unmasking of occult diabetes.3,4,11 It may reflect a nonspecific response to brain ischemia or damage to a specific central location. Although previous studies have linked hyperglycemia and stroke size, these have not evaluated whether infarct location is specifically linked to glucose level.

The insular cortex (IC) is a site with autonomic efferent projections.14 Stimulation and damage to the insula have been shown to clinically and experimentally have a number of autonomic effects, including an elevation of sympathoadrenal tone and sudden cardiac death.15,16 Therefore, damage to the insula may result in elevated glucose levels in the context of...
sympathoadrenal dysregulation. Using MRI and glucose measurements, we tested the hypothesis that acute ischemia of the IC is associated with admission hyperglycemia.

Methods

Patients
Thirty-one patients presenting with anterior circulation ischemic stroke syndromes within 24 hours of symptom onset were included. Stroke onset was taken as the time neurological dysfunction was first observed. When patients awoke with symptoms, were unable to communicate, or were unaware of their deficits, onset time was regarded as the time they were last known to be symptom-free. All patients had a National Institutes of Health Stroke Scale (NIHSS) score of \( \geq 4 \) and a premorbid modified Rankin score of \( \leq 2 \). Patients with a history of previous stroke or contraindication to MRI were excluded. Patients were excluded from analysis if there was resolution of their neurological syndrome or no measurable diffusion-weighted lesion.

Plasma glucose and HbA\(_1c\) were measured on admission. Subjects were included regardless of glucose level. The presence of prestroke diabetes was based on the reported history or treatment with hypoglycemic agents. Time to glucose testing was measured from the time of stroke onset to sample receipt into the laboratory. Acute stress hyperglycemia was defined as an elevation of blood glucose level \( (>8 \text{ mmol/L}) \) in the presence of normal HbA\(_1c\) \((<6.2\% )\) regardless of diabetes status. Human Research Ethics Committee approval and informed consent was obtained for all patients.

MRI Protocol

MRI studies were performed at admission and on days 3 through 5 (subacute) using a 1.5-T echo planar imaging (EPI)-equipped whole-body scanner (Signa Horizon SR120; General Electric). Sequences included a T1-weighted sagittal localizer and diffusion-weighted imaging (DWI) obtained using a multislice, single-shot spin-echo EPI sequence with 16 6-mm plus 1-mm gap slices. Matrix size was 256×256, field of view 40×40 cm, and repetition time/echo time 6000/107 ms. Diffusion gradient strength was varied between 0 and 22 mT/m, resulting in 3 \( b \) values of increasing magnitude from 0 to 1000 s/mm. Isotropic DWI images were obtained by averaging the signal from all orthogonal directions with the highest diffusion weighting \( (b=1000) \).

Image Analysis

Volumetric analysis of DWI lesions was performed with Medx Software (Sensor Systems) by outlining regions of interest (ROIs) on each image using a semiautomated pixel-wise thresholding technique. ROIs and planimetric volume measurements were determined by a single investigator blinded to all clinical data. The intraobserver and interobserver variability for DWI lesion volume measurement within our group is \( <5\% \). The IC was identified on the acute T2-weighted images \( (b=0; \text{DWI}) \). It was defined anatomically as the region of cortical gray matter at the base of the Sylvian fissure medial to the frontoparietal and temporal opercula. The flow void of the middle cerebral artery, located on its surface, was used to divide the insula into anterior and posterior portions. Insular cortical lesion involvement was dichotomized on a yes/no basis by 2 investigators blinded to all clinical data \( (k=0.87) \).

Statistical Analysis

Multivariate linear regression was used to assess the effect of acute insular cortical ischemia, acute and subacute DWI lesion volume, time to glucose measurement, pre-existing diabetes, age, systolic blood pressure, HbA\(_1c\), and NIHSS on admission glucose level. Glucose and DWI volume values were log transformed. HbA\(_1c\), age, systolic blood pressure, NIHSS, and time to glucose measurement were assessed as continuous variables. Variables were retained in the final model if they appeared to be significant explanatory factors \( (P<0.05) \) or potential confounders. Standard regression diagnostics were used to assess linear regression assumptions and to identify potentially influential observations in the data set. There was no evidence of interaction between covariates, and no individual observations appeared to exert undue influence, particularly in relation to the estimated effect of insular involvement.

The effect of each explanatory variable is expressed as the estimated ratio of glucose level per unit increase in the explanatory variable. The effect of DWI lesion volume is given in terms of the ratio of glucose level for every doubling of DWI lesion volume. Statistical analysis was performed using Stata Version 7.0 (StataCorp).

Results

Patient Characteristics

The median interval between stroke onset and MRI was 13 hours (range 3 to 23). Admission hyperglycemia was present in 11 of 31 (35%) patients. Of these hyperglycemic patients, 5 (45%) had pre-existing diabetes and elevated HbA\(_1c\), 2 (18%) had pre-existing diabetes and a normal HbA\(_1c\), and 4 (36%) were nondiabetic with a normal HbA\(_1c\). Therefore, on the basis of our definition, 6 patients (55%) had acute stress hyperglycemia. Six of the 20 normoglycemic patients had pre-existing diabetes. Fourteen patients had DWI abnormalities involving the IC (IC+) and 17 did not (IC−). The patient characteristics categorized as IC+ and IC− are summarized in Table 1. Representative DWI examples are shown in Figure 1. The median time interval between stroke onset and admission blood glucose measurement was 7.5 hours (range 1.5 to 18) for IC+ patients and 13 hours (1.5 to 24) for IC− patients \( (P=0.17) \).

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Data</th>
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<tr>
<td></td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Stroke hemisphere, left:right</td>
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<tr>
<td>Pre-existing diabetes, n</td>
</tr>
<tr>
<td>Acute studies, n=31</td>
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<tr>
<td>Admission HbA(_1c), %</td>
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<td>Admission systolic blood pressure</td>
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<td>Admission NIHSS</td>
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<td>Admission blood glucose, mmol/L</td>
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<tr>
<td>DWI lesion volume, mL</td>
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<tr>
<td>Subacute studies, n=30*</td>
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<td></td>
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<tr>
<td>DWI lesion volume, mL</td>
</tr>
</tbody>
</table>

*Data are expressed as median (range).

IC+ patients had significantly higher median admission glucose levels \( (8.6 \text{ mmol/L}) \) compared with IC− patients \( (6.5 \text{ mmol/L}; P=0.006) \). Median acute DWI lesion volume was significantly larger in the IC+ group \( (13 \text{ mL}) \) compared with the IC− group \( (3 \text{ mL}; P=0.003) \). Of those patients with insular involvement, the incidence of hyperglycemia \( (>8 \text{ mmol/L}) \) was 60% \( (3 \text{ of 5} \text{ patients}) \) in those with left-sided lesions and 66% \( (6 \text{ of 9} \text{ in those with right-sided lesions}) \). Although there were more right-sided insular infarcts in the IC+ group, the proportion with hyperglycemia was similar.
Nine patients had DWI abnormalities involving the entire IC and 5 involving the posterior insula only. Every patient in the posterior insular group had an admission glucose of $\leq$11.350 mmol/L. Median admission blood glucose level was similar in patients with entire insular ischemia (7.3 mmol/L, range 5.5 to 17.0) and those with posterior insular ischemia only (9.4 mmol/L, range 8.2 to 15.9; $P$=0.167). This occurred despite the fact that patients with ischemia of the entire IC had significantly larger DWI volumes (median 50 mL, range 7 to 148) compared with those with ischemia of the posterior insula only (5 mL, range 3 to 12; $P$=0.003; see Figure 3). One patient with isolated involvement of the anterior insula had a glucose of 5.3 mmol/L.

**Acute Stroke Severity**

The distribution of admission NIHSS values was bimodal, with a median value of 14 (range 3 to 26). There was a strong correlation between admission NIHSS and DWI volume (Spearman $\rho$=0.572; $P$<0.01). There was also a correlation between NIHSS and glucose level (Spearman $\rho$=0.398; $P$=0.027).

**Hyperglycemia Predictors**

The results of the final multiple regression model are shown in Table 2. Univariate regression indicated a weak relationship between DWI volume and admission glucose (ratio=1.03 per doubling of DWI volume; 95% CI, 0.983 to 1.089; $P$=0.188; Figure 2A). However, after controlling for the effect of insular cortical ischemia on multiple regression, there was no association between acute DWI infarct volume

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Table 2. Final Multivariate Regression Model Showing the Effect of Each Variable on Acute Glucose Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ratio*</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insular cortex involve</td>
<td>1.392</td>
<td>1.166–1.660</td>
<td>0.001</td>
</tr>
<tr>
<td>Pre-existing diabetes mellitus</td>
<td>1.284</td>
<td>1.074–1.535</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic blood pressure (per 10 mm Hg)</td>
<td>1.071</td>
<td>1.031–1.112</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>0.886</td>
<td>0.801–0.980</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*Adjusted geometric mean ratio representing the expected proportional change in glucose associated with each variable.

$R^2$ for the model, 0.620; $R^2$ for IC alone, 0.231.

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Figure 1. Diffusion-weighted images. A, Diabetic patient: glucose 17 mmol/L and a large DWI lesion volume (130 mL) involving the entire IC. B, Nondiabetic patient: glucose 8.3 mmol/L and a small DWI lesion volume (4 mL) involving the posterior insula only. C, Diabetic patient: glucose 6.7 mmol/L and a moderate DWI lesion volume (22 mL) sparing the IC.

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Figure 2. The apparent association between log (ln) admission glucose level and DWI volume on univariate analysis (A) disappears after controlling for the effect of insular cortical ischemia (B). At any given infarct volume, IC+ patients (circles, solid line) had glucose levels 1.4× higher than IC− patients (triangles, broken line).
and glucose (Figure 2B). Admission glucose levels were only 1.004× higher for every doubling in DWI lesion volume (95% CI, 0.9614 to 1.0487; P=0.849). At any given infarct volume, whether large or small, IC+ patients had glucose values 1.392× higher than IC− patients (P=0.001). The relationship between insular ischemia and hyperglycemia was independent of all other variables in the multiple regression model, including diabetes and NIHSS.

Patients with pre-existing diabetes had glucose values 1.284× higher than nondiabetics (P=0.008). Glucose values increased 1.071-fold for every 10 mm Hg increase in systolic blood pressure (P=0.001). Increasing age was associated with a decrease in glucose level, corresponding to a ratio of 0.89 per 10 years of age (P=0.017). The time interval to glucose measurement was shorter for IC+ patients; however, it was not an independent predictor of admission glucose level on multiple regression (ie, the observed increase in glucose values for the IC+ group was not explained by earlier glucose measurement).

Admission glucose levels increased only 1.010× for every unit increase in NIHSS (ratio=1.010; 95% CI, 0.997 to 1.024; P=0.133). Including NIHSS in the regression model did not alter the effect of insular ischemia on glucose levels. There was no evidence of an association between HbA1c and glucose level (ratio=1.012 per percentage unit increase in HbA1c; 95% CI, 0.942 to 1.088; P=0.849). Patients with an elevated HbA1c who were IC+ had higher glucose levels than IC− patients at any given HbA1c value, suggesting there may also be a “stress response” in patients with prestroke hyperglycemia (ie, elevated HbA1c).

Subacute DWI Studies
Thirty patients were reimaged on days 3 through 5 (1 IC+ patient died). DWI lesion volumes remained larger in the IC+ group (Table 1). The median ratio of subacute to acute DWI volume was 2.26 (range 0.53 to 83.51). When controlling for the effect of insular ischemia using multiple regression, the ratio of glucose per doubling of subacute DWI lesion volume was only 1.014 (95% CI, 0.977 to 1.052; P=0.448).

Discussion
This is the first study to demonstrate that acute ischemia of a specific cortical region, namely the IC, may contribute to poststroke hyperglycemia. Furthermore, this is independent of DWI infarct volume, pre-existing glycemic status, and clinical stroke severity.

Poststroke Acute Stress Hyperglycemia
Experimental animal models indicate that the level of plasma glucose at the time of focal cerebral ischemia is an important determinant of brain injury. As early as 1976, Melamed demonstrated that a significant proportion of stroke patients develop hyperglycemia as part of a “stress response.” We defined stress hyperglycemia as an elevated blood glucose level in the presence of a normal HbA1c, regardless of diabetes status. The incidence of stress hyperglycemia in our study was 19%, consistent with previous studies. As a measure of glucose homeostasis, HbA1c value has been used to estimate prestroke glycemic status. We found no relationship between HbA1c and admission blood glucose level, consistent with the hypothesis that an acute stress response underlies the hyperglycemia observed in some stroke patients. Prestroke glycemic status has not been found to predict stroke severity and mortality in most studies. It has been suggested that the degree of hyperglycemia reflects the severity of the cerebral insult. In our study, acute NIHSS was used as a measure of stroke severity. There was an association between stroke severity and hyperglycemia that was also suggested by multiple regression. However, the effect of insular cortical ischemia on acute glucose level was independent of stroke severity.

The term stress hyperglycemia implies a transient phenomenon, and its duration remains controversial. A modest increase in blood glucose level is most likely to occur within the first 6 hours of stroke onset. Poststroke glucose levels then decline spontaneously during subsequent hours in the absence of therapy directed at normoglycemia. Whether poststroke glucose samples are collected randomly, after fasting, and with or without an oral glucose tolerance test remains controversial, and methodological superiority in quantifying abnormal glucose homeostasis after stroke has not been demonstrated. Clearly defining the temporal profile of stress hyperglycemia has implications for the duration of proposed glucose-lowering therapies after stroke.

Central Control of Glucose Homeostasis and the Stress Response
There is evidence that stress hyperglycemia is a central phenomenon. The hypothalamic–pituitary–adrenal axis is integral to this neuroendocrine stress response. Implicated in the pathogenesis is an increase in sympathetic nervous system activity. The hypothalamus is the most studied central site with respect to glucose metabolism. Animal studies have shown that stimulation of the hypothalamus results in hyperglycemia. Although a cortical site responsible for governing glucose homeostasis is presumed to exist, a specific location has never been identified. The IC is interconnected with subcortical autonomic centers including the hypothalamus. The insula has been demonstrated to be a cortical region that can influence autonomic function and, in particular, sympathetic nervous system tone. Clinical studies of insular cortical stroke have documented an elevation of sympathetic nervous system activity, increased serum catecholamines, ECG abnormalities, and myocardial injury. Previous studies have demonstrated lateralization of autonomic function within the cerebral hemispheres. We found no evidence of insular lateralization with respect to hyperglycemia. Given the evidence for the role of the IC in autonomic nervous system regulation, it is possible that the hyperglycemia in our patients is part of a more generalized elevation in sympathetic tone, possibly mediated by the abolition of inhibitory cortical control mechanisms.

IC and Infarct Volume
In our study, patients with insular cortical ischemia, regardless of acute or subacute infarct volume, had significantly
However, patients with insular cortical ischemia, regardless of infarct size, had admission glucose values $1.4 \times$ greater than those without. This relationship was both statistically significant and independent of infarct volume.

There are a number of limitations to our study. The small sample size mandates confirmation of our findings and limits the ability of this study to detect any effect of hemispheric lateralization on stress hyperglycemia. There is also a lack of other indices of an acute stress response such as cortisol or noradrenaline that is currently being addressed in a larger prospective study. Although our results do not establish cause and effect, they do provide evidence to support the hypothesis that insular cortical dysfunction may play a pathophysiological role in the production of poststroke hyperglycemia as 1 aspect of an acute stress response.

**Conclusion**

The IC is the first cortical site found to be associated with poststroke hyperglycemia. This relationship is independent of pre-existing glycemic status, stroke severity, and infarct volume. This suggests that IC injury may result in acute dysregulation of glucose metabolism consistent with a stress response. Therefore, future studies of poststroke hyperglycemia should account for the effect of insular cortical ischemia.

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**References**


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